## REMARKS/ARGUMENTS

***Status of the Claims***

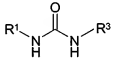
Claims 46-53 are pending.

***Rejections under 35 U.S.C. § 102***

Rejection under 35 U.S.C. § 102(b) over JP 07304755 ("Ichihara")

The Office has maintained the rejection of claims 46 and 48 as allegedly anticipated by Ichihara. This rejection is traversed for the reasons discussed in the previous responses to Office Actions and set forth below.

As the Office is aware, anticipation requires that the cited reference disclose or suggest each and every element or step recited in the rejected claim. M.P.E.P. § 2131. The present methods require administering a therapeutically effective amount of a compound (i) that has the structure




wherein $R^1$ and $R^3$ are each independently selected from the group consisting of $C_1$-$C_{20}$ substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic; and (ii) functionally is an inhibitor of soluble epoxide hydrolase ("sEH"). Here, the Office concedes that Ichihara is silent about the functional characteristic of the condensation diazepine derivative compounds to inhibit sEH, but alleges that such property or characteristic is inherent in the compounds disclosed by Ichihara. *See, e.g.*, page 9 of the Office Action mailed on December 29, 2005 and page 11 of the Office Action mailed on August 23, 2006. The Office further alleges that Applicants simply discovered a new pharmacological mechanism (sEH inhibiting activity) for a prior art compound represented by the claimed structure which is directed to the same ultimate purpose. *See*, page 6 of the Office Action.

The Burden for Inherent Anticipation Has Not Been Met.

The Office has not met its burden for alleging inherent anticipation of the claimed methods based on the disclosure of Ichihara. According to the M.P.E.P., "[t]he fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic (emphasis in original; *citing In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) and *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)). *See*, M.P.E.P. § 2112 (IV). The M.P.E.P. goes on to quote *In re Robertson* as stating "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is ***necessarily present*** in the thing described in the reference, ***and that it would be so recognized by persons of ordinary skill***. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient' " (emphasis added; *quoting In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). *Id.* The M.P.E.P. reiterates the standard for establishing a rejection of inherent anticipation by quoting *Ex parte Levy* as stating "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the teachings of the applied prior art." (emphasis in original; *quoting Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

Here, the Office concedes that Ichihara is silent as to the whether the disclosed compounds inhibit sEH. *See, e.g.*, page 9 of the Office Action mailed on December 29, 2005 and page 11 of the Office Action mailed on August 23, 2006. Therefore, any alleged functional properties of the condensation diazepine derivative compounds of Ichihara to inhibit an sEH enzyme is ***not necessarily present***. Furthermore, those of skill in the art do not recognize that the compounds disclosed in Ichihara ***necessarily*** possess the functional the functional characteristic, as is required to properly establish a rejection of inherent anticipation.

First, Ichihara discloses that their condensation diazepine derivative compounds are specific and powerful inhibitors of human renin.[1] A BLAST alignment of the amino acid sequences of human renin (GenBank accession number AAA60363) and human sEH (GenBank

accession number AAG14968) shows that the proteins are structurally disparate proteins, sharing no significant sequence homology.[2] Second, human renin and human sEH do not share commonly conserved protein structural domains. Whereas human sEH has the conserved domains alpha/beta hydrolase ("Abhydrolase_1," pfam00561) and a hydrolase superfamily domain COG1011, human renin has the conserved domains A1_propeptide (pfam07966) and eukaryotic aspartyl protease ("Asp," pfam00026). Not surprisingly, BLAST searches inputting a human renin amino acid sequence do not retrieve any human sEH sequences, and BLAST searches inputting a human sEH amino acid sequence do not retrieve any human renin sequences.[3] In view of the lack of structural relation of human renin and human sEH proteins, those of skill would expect that compounds that inhibit the function of renin are unlikely to inhibit the enzymatic activity of sEH. Likewise, those of skill would expect that compounds that inhibit the enzymatic activity of sEH are unlikely to inhibit the function of renin, regardless of a common urea or thiourea pharmacophore.

This is confirmed by the Rule 132 Declarations submitted by Dr. Bruce Hammock on June 13, 2006 and February 23, 2007. Dr. Hammock's Declarations summarize his understanding of the structural requirements of urea inhibitors of sEH based on an evaluation of the structure-activity relationship of at least 2000 of different compounds for sEH inhibitory activity. Dr. Hammock attests in his Declaration submitted on June 13, 2006 that a urea pharmacophore in itself is not sufficient for a compound to ***necessarily*** have the function of inhibiting an sEH at pharmacologically relevant concentrations. For example, based on the crystal structure of the human sEH enzyme and extensive structure-activity determinations, bulky or polar groups near the urea result in compounds that do not inhibit sEH. *See*, paragraphs 6-8 of the Rule 132 Declaration submitted on June 13, 2006. With respect to the specific condensation diazepine derivative compounds disclosed by Ichihara, Dr. Hammock attests that they are unlikely to effectively inhibit a sEH because the 7-membered heterocyclic ring

[1] A machine translation of the full text of JP7-304755 is provided as Exhibit A.
[2] Copies of GenBank entries AAA60363 and AAG14968, and their BLASTp pairwise alignment analysis are attached as Exhibit B.
[3] Copies of BLAST searches inputting the amino acid sequences of human renin or human soluble epoxide hydrolase, and the identified conserved domains of these proteins, are provided as Exhibit C.

comprising the requisite diazepine substituent attached to the urea is too bulky and polar to bind to the catalytic site of the enzyme. *See*, *id* at paragraphs 10-11. Dr. Hammock recognizes and attests that the condensation diazepine compounds of Ichihara are designed to target a different molecule (*i.e.*, renin), and that the compounds would be inactive as inhibitors of sEH. *Id.* at paragraph 11.

Therefore, those of skill recognize that the condensation diazepine derivative compounds disclosed by Ichihara are unlikely to inhibit sEH activity rather than ***necessarily*** inhibit sEH activity, as required to meet the standard for inherent anticipation. Ichihara discloses that the condensation diazepine derivative compounds are specific and powerful inhibitors of renin, a protein that is structurally disparate from sEH. Those of skill will readily recognize the structural and functional unrelatedness of renin and sEH. Dr. Hammock's Declaration confirms that the condensation diazepine derivative compounds disclosed by Ichihara are unlikely to inhibit sEH activity rather than ***necessarily*** inhibit sEH activity. Accordingly, unlike that alleged by the Office, Applicants did not discover a new pharmacological mechanism (sEH inhibiting activity) for compounds disclosed in Ichihara because these compounds are unlikely to have such activity. Rather, Applicants discovered a new method of treating hypertension with sEH inhibitors that have a urea pharmacophore.

Moreover, as to Claims 46-53, these claims require that the patient is administered with "a therapeutically effective amount of an inhibitor of sEH". This recitation is a claim limitation requiring that the compound administered is an inhibitor of sEH and that it is administered in an amount to be therapeutically effective. Accordingly, any compounds which would not function as an sEH inhibitor would necessarily be excluded from the claimed invention.

The Office has attempted to shift the burden of proving the absence of inherent anticipation onto Applicants without first showing a sound basis for believing that the compounds of the present methods and the compounds used by Ichihara are the same. *See*, M.P.E.P. § 2112.01. The Office has not met this burden to establish inherent anticipation. Regardless, Applicants have rebutted any alleged *prima facie* case of inherent anticipation by providing evidence showing that the compounds disclosed in Ichihara do not ***necessarily*** possess

the characteristics of the compounds in the claimed methods. Even possessing a common urea or thiourea pharmacophore, the condensation diazepine derivative compounds disclosed by Ichihara, which have the function of inhibiting renin, are structurally and functionally distinct from the sEH inhibitors used in the present methods. The BLAST alignments showing the unrelated structure of renin and sEH, the Declarations of Dr. Hammock, and the disclosure of Ichihara itself all support Applicants' assertion that the condensation diazepine derivative compounds disclosed by Ichihara do not ***necessarily*** possess the functional characteristic of inhibiting sEH, a required attribute of the compounds in the claimed methods. Accordingly, the standard for asserting inherent anticipation has not been met.

Ichihara does not Disclose or Suggest Any Nexus between sEH Inhibitors and Reducing Blood Pressure or Hypertension

The Office is respectfully reminded that the present invention is directed to ***methods*** of reducing blood pressure or reducing hypertension in a patient by administering a therapeutically effective amount of an inhibitor of sEH. The invention is based in part on the discovery of the nexus between the inhibition of sEH and the therapeutic benefit of reduced blood pressure and/or hypertension. Ichihara does not disclose or suggest anything regarding inhibiting sEH, much less identify a nexus between the inhibition of sEH and the therapeutic benefit of reduced blood pressure and/or hypertension. Instead, Ichihara discloses methods of specifically and powerfully inhibiting renin.

In view of the foregoing, Ichihara does not anticipate the present methods, either expressly or inherently. Accordingly, the Office is respectfully required to withdraw the present rejection.

Rejection under 35 U.S.C. § 102(e) over U.S. Patent No. 5,962,455 ("Blum")

The Office has maintained the rejection of claims 46 and 48 under 35 U.S.C. § 102(e) as allegedly anticipated by Blum. This rejection is traversed for the reasons discussed in the previous responses to Office Actions and set forth below.

Blum Does Not Disclose Compounds with Both Urea Substituents Being $C_1$-$C_{20}$

As an initial matter, Applicants reiterate the assertion that Blum does not disclosure or suggest use of a compound comprising urea pharmacophore wherein $R^1$ and $R^3$ are each independently $C_1$-$C_{20}$. The Office does not dispute this interpretation of the compounds disclosed in Blum. Instead, the Office alleges that there is no indication in the instant claims 46 and 48 that $R^1$ or $R^3$ must be essentially $C_1$-$C_{20}$. *See*, page 7 of the Office Action mailed on February 7, 2008. This is incorrect.

Both claims 46 and 48 recite the clause

**"... wherein $R^1$ and $R^3$ are each independently selected from the group consisting of $C_1$-$C_{20}$ substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic."**

This clause is an affirmative structural limitation on the sEH inhibitors used in the present methods that limits the $R^1$ and $R^3$ substituents on both sides of the urea core to $C_1$-$C_{20}$, regardless of whether it is a substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic. It is improper for the Office to ignore or disregard an express structural limitation, such as the ones recited in both claims 46 and 48.

Applicants reiterate their position that because Blum discloses compounds wherein at least one of the R groups, $R^1$ or $R^3$, must be greater than 20 carbons, Blum does not anticipate the present methods.

The Burden for Inherent Anticipation Has Not Been Met.

Even assuming *arguendo* that the phrase "$C_1$ to $C_{20}$" qualifies only the term "alkyl", the Office concedes that Blum is silent about the functional characteristic of the substituted benzylamine derivative compounds to inhibit sEH, but alleges that such property or characteristic is inherent in the compounds disclosed by Blum. *See, e.g.*, page 10 of the Office Action mailed on December 29, 2005 and page 11 of the Office Action mailed on August 23, 2006.

For the reasons similar to those set forth for Ichihara, above, the Office has not met the burden for alleging inherent anticipation of the claimed methods based on the disclosure of Blum.

First, Blum discloses that their substituted benzylamine derivative compounds selectively bind to mammalian neuropeptide Y1 receptors (NPY1R) and inhibit the activity of neuropeptide Y. A BLAST alignment of the amino acid sequences of human NPY1R (GenBank accession number AAS55647) and human sEH (GenBank accession number AAG14968) shows that they are structurally disparate proteins, sharing no significant sequence homology.[4] Moreover, human NPY1R and human sEH do not share commonly conserved protein structural domains. Whereas human sEH has the conserved domains alpha/beta hydrolase ("Abhydrolase_1," pfam00561) and a hydrolase superfamily domain COG1011, human NPY1R has the conserved domain for 7 transmembrane receptors (rhodopsin family) ("7tm_1," pfam00001). Not surprisingly, BLAST searches inputting a human NPY1R amino acid sequence do not retrieve any human sEH sequences.[5] As shown in Exhibit C, BLAST searches inputting a human sEH amino acid sequence do not retrieve any human NPY1R sequences. In view of the structural unrelatedness of human NPY1R and human sEH proteins, those of skill would expect that compounds that bind to NPY1R and interfere with the function of neuropeptide Y are unlikely to inhibit the enzymatic activity of sEH. Likewise, those of skill would expect that compounds that inhibit the enzymatic activity of sEH are unlikely to bind to NPY1R, regardless of a common urea or thiourea pharmacophore.

This is confirmed by the Rule 132 Declarations submitted by Dr. Bruce Hammock on June 13, 2006 and February 23, 2007. With respect to the specific substituted benzylamine derivative compounds disclosed by Blum, Dr. Hammock attests that they are unlikely to effectively inhibit an sEH because at least one of the substituents (*i.e.*, the substituent that has more than 20 carbons) is too bulky to inhibit the catalytic site of the sEH enzyme. *See*, paragraphs 12-13 of the Rule 132 Declaration of Dr. Hammock submitted on June 13, 2006.

[4] Copies of GenBank entries AAS55647 and the BLASTp pairwise alignment to soluble epoxide hydrolase are attached as Exhibit D.

[5] Copies of BLAST searches inputting the amino acid sequences of human NPY1R, and the identified conserved domains, are provided as Exhibit E.

Dr. Hammock recognizes and attests that the substituted benzylamine derivative compounds of Blum are designed to target a different molecule (*i.e.*, NPY1R), and that they would be inactive as inhibitors of sEH. *Id.* at paragraph 13.

Therefore, those of skill would recognize that the substituted benzylamine derivative compounds disclosed by Blum are unlikely to inhibit sEH activity rather than ***necessarily*** inhibit sEH, the standard required for inherent anticipation. Blum discloses that the substituted benzylamine derivative compounds selectively bind to NPY1R, a protein that is structurally disparate from sEH. Those of skill will readily recognize the structural and functional unrelatedness of NPY1R and sEH. Dr. Hammock's Declaration confirms that the substituted benzylamine derivative compounds disclosed by Blum are unlikely to inhibit sEH activity rather than ***necessarily*** inhibit sEH.

As before and as it relates to Claims 46-53, these claims require that the patient is administered with "a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase" (sEH). This recitation is a claim limitation requiring that the compound administered is an inhibitor of sEH and that it is administered in an amount to be therapeutically effective. Accordingly, any compounds which would not function as an sEH inhibitor would necessarily be excluded from the claimed invention.

The Office has again attempted to shift the burden of proving the absence of inherent anticipation onto Applicants without first showing a sound basis for believing that the compounds of the present methods and the compounds used by Blum are the same. *See*, M.P.E.P. § 2112.01. Like with Ichihara, the Office has not met this burden to establish inherent anticipation. Regardless, Applicants have rebutted any alleged *prima facie* case of inherent anticipation by providing evidence showing that the compounds disclosed in Blum do not ***necessarily*** possess the characteristics of the compounds in the claimed methods. Even possessing a common urea or thiourea pharmacophore, the substituted benzylamine derivative compounds disclosed by Blum, which have the function of binding to NPY1R, are structurally and functionally distinct from the sEH inhibitors used in the present methods. The BLAST alignments showing the unrelated structure of NPY1R and sEH, the Declarations of Dr. Hammock, and the disclosure of Blum itself, all support Applicants' assertion that the

substituted benzylamine derivative compounds disclosed by Blum do not ***necessarily*** possess the functional characteristic of inhibiting sEH, a required attribute of the compounds in the claimed methods. Accordingly, the standard for asserting inherent anticipation has not been met.

Blum does not Disclose or Suggest Any Nexus between sEH Inhibitors and Reducing Blood Pressure or Hypertension

As with Ichihara, Blum does not disclose or suggest anything regarding inhibiting sEH, much less identify a nexus between the inhibition of sEH and the therapeutic benefit of reduced blood pressure and/or hypertension. Instead, Blum discloses methods of inhibiting the function of neuropeptide Y by employing compounds designed to selectively binding to NPY1R.

In view of the foregoing, Blum does not anticipate the present methods, either expressly or inherently. Accordingly, the Office is respectfully required to withdraw the present rejection.

***Rejections under 35 U.S.C. § 103(a)***

Rejection under 35 U.S.C. § 103(a) over JP 07304755 ("Ichihara")

The Office has rejected claims 50-53 under 35 U.S.C. § 103(a) as allegedly rendered obvious by Ichihara. This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143.

Here, Ichihara does not disclose or suggest any method of reducing blood pressure or reducing hypertension by inhibiting sEH at all, much less with a compound that inhibits sEH activity with an $IC_{50}$ of less than 500 μM or less than 17.8 μM. In attempting to formulate this rejection, the Office relies on the improper reasoning set forth in alleging inherent anticipation. The Office concedes that Ichihara does not disclose the compounds that exhibit

specific epoxide hydrolase enzymatic activity with an $IC_{50}$ of less than 500 μM or less than 17.8 μM. *See*, page 4 of the Office Action mailed on February 7, 2008. This is because, as discussed above, Ichihara does not contemplate any nexus between inhibiting sEH and the therapeutic benefit of reducing blood pressure or reducing hypertension. Instead, Ichihara selected for and discloses compounds that specifically and powerfully inhibit renin, a protein that is structurally completely disparate from sEH. It follows that the compounds disclosed in Ichihara are structurally and functionally different from the sEH inhibitors used in the present methods, even if they share a urea or thiourea pharmacophore. To the extent that the condensation diazepine derivative compounds disclosed by Ichihara inhibit sEH at all, they do not inhibit sEH activity with an $IC_{50}$ of less than 500 μM or less than 17.8 μM. Without identifying any reason to inhibit sEH, Ichihara certainly did not select for compounds that specifically inhibit sEH at micromolar concentrations, *e.g.*, with an $IC_{50}$ of less than 500 μM or less than 17.8 μM.

Still further, any rejection which is predicated upon "inherent obviousness" is simply in error. As quoted with acceptance in *In re Rijckaert*, *supra*, at page 1957:

> ..."That which is inherent is not necessarily known.
> Obviousness cannot be predicated on what is unknown."
> (citations omitted)

Such is the case here. The sEH inhibition of the compounds of Claims 50-53 as they relate to treatment methods for reducing hypertension and reducing blood pressure were unknown prior to the claimed invention. Accordingly, to reject such claims based on what was unknown is improper.

In view of the foregoing, Ichihara does not render the present methods obvious. Accordingly, the Office is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 103(a) over U.S. Patent No. 5,962,455 ("Blum")

The Office has rejected claims 50-53 under 35 U.S.C. § 103(a) as allegedly rendered obvious by Blum. This rejection is respectfully traversed.

Here, Blum does not disclose or suggest any method of reducing blood pressure or reducing hypertension by inhibiting sEH at all, much less with a compound that inhibits sEH activity with an $IC_{50}$ of less than 500 μM or less than 17.8 μM. Furthermore, as discussed above, the compounds of Blum require that at least one substituent attached to the urea pharmacophore have more than 20 carbons. In attempting to formulate this rejection, the Office relies on the improper reasoning set forth in alleging inherent anticipation. The Office concedes that Blum does not disclose the compounds that exhibit specific epoxide hydrolase enzymatic activity with an $IC_{50}$ of less than 500 μM or less than 17.8 μM. *See*, page 4 of the Office Action mailed on February 7, 2008. This is because, as discussed above, Blum does not contemplate any nexus between inhibiting sEH and the therapeutic benefit of reducing blood pressure or reducing hypertension. Instead, Blum selected for and discloses compounds that specifically and powerfully inhibit NPY1R, a protein that is structurally completely disparate from sEH. It follows that the compounds disclosed in Blum are structurally and functionally different from the sEH inhibitors used in the present methods, as pointed out in the present and previous response, even if they share a urea or thiourea pharmacophore. To the extent that the substituted benzylamine derivative compounds disclosed by Blum inhibit sEH at all, they do not inhibit sEH activity with an $IC_{50}$ of less than 500 μM or less than 17.8 μM. Without identifying any reason to inhibit sEH, Blum certainly did not select for compounds that specifically inhibit sEH at micromolar concentrations, *e.g.*, with an $IC_{50}$ of less than 500 μM or less than 17.8 μM.

As discussed above regarding the disclosure of Ichihara, any rejection which is predicated upon "inherent obviousness" is simply in error. As quoted with acceptance in *In re Rijckaert*, *supra*, at page 1957:

> ..."That which is inherent is not necessarily known.
> Obviousness cannot be predicated on what is unknown."
> (citations omitted)

Such is the case here. The sEH inhibition of the compounds of Claims 50-53 as they relate to treatment methods for reducing hypertension and reducing blood pressure were

unknown prior to the claimed invention. Accordingly, to reject such claims based on what was unknown is improper.

In view of the foregoing, Blum does not render the present methods obvious. Accordingly, the Office is respectfully requested to withdraw this rejection.

***Allowable Subject Matter***

The Examiner is thanked for indicating that claims 47 and 49 are allowable.

**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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